Copper-Induced Ammonia N-H Functionalization

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The activation of ammonia has been achieved with the aid of the TpM6Cu core (TpM6 = hydrotris(3-mesityl-pyrazolyl)borate) Complexes of general composition TpM6Cu(amine) (1-4) including the ammonia adduct TpM6Cu(NH3) (1) have been synthesized and fully spectroscopic- and structurally characterized. Coordinated ammonia in 1 has been reacted with Ph3CP2 yielding TpM6Cu(NH2CPPh3) (5) as the result of N-H cleavage and N-C bond formation. In a parallel manner the catalytic functionalization of ammonia with ethyl diazoacetate leading to glycinate derivatives has been developed with TpM6Cu(THF) as the catalyst, in the first example of this transformation with a copper-based system.

Results and Discussion

Synthesis and characterization of TpM6Cu(NH3) (1).

The ammonia adduct TpM6Cu(NH3) (1) has been synthesized using TpM6Cu(THF) as the starting material, following a procedure already described for other olefin or alkyne TpM6 copper adducts in our group (eqn (1)). Ammonia gas was bubbled through a colourless solution of TpM6Cu(THF) in dichloromethane for 15-20 min, and the solution was then stored in the freezer at -30 °C from which colourless crystalline material was collected in 95% isolated yield after three successive crops. The formulation of this compound as TpM6Cu(NH3) (1) came straightforwardly from its spectroscopic and analytical data. For instance, the 1H NMR spectrum showed the typical resonances of the coordinated TpM6 ligand with one signal for each independent nucleus of the pyrazolyl moiety, as the result of a local C3v symmetry that makes the

Introduction

The activation of the N-H bonds of ammonia yet constitutes a challenge for current chemistry, particularly in the context of metal-catalysed (hydro)amination reactions.1 Ammonia can coordinate a number of transition metals, and subsequent reactivity may lead to amido, imido (nitrile) and even nitrido complexes, that could serve as intermediates in catalytic cycles.2,3 During the last decade a family of tetracoordinate complexes bearing the TpCu moiety (TpC = hydrotrispyrazolylborate ligand) and a fourth donor ligand such as CH2CN, CO, PR3 alkene or alkyne has been developed (Scheme 1). The use of TpM6 [hydrotris(3-mesitylpyrazolyl)borate] provided interesting features to those complexes due to the interaction between the aryl rings with olefin/alkyne ligands. Interestingly, we found that in spite of the large number of TpCuL complexes reported to date, the ammonia derivative remained yet undescribed. With this idea in mind, we started this work that has led to the synthesis and structural characterization of TpM6Cu(NH3), as well as a series of related TpM6Cu(NR3) for comparative purposes. The availability of the ammonia adduct has allowed the study of the reactivity of the N-H bonds, from which we have observed N-H bond cleavage and subsequent N-C bond formation in a process that provides a net NH functionalization. Additionally, in a parallel manner, the catalytic functionalization of ammonia upon insertion of CH2COEt carbene units (from ethyl diazoacetate, Et2CHCO2Et, EDA) has been achieved employing TpM6Cu(THF) as the catalyst. The latter has only been described to date with iron-based catalysts,9 the current work constituting, to the best of our knowledge, the first example of a copper-catalysed ammonia functionalization with this strategy, since previous examples with this metal being were described only with substituted amines.10

Scheme 1. Previously described TpCuL complexes.
three pyrazolyl rings equivalents. In addition, a broad singlet located at δ 0.59 ppm that integrated for 3H has been assigned to coordinated NH₃. The IR spectrum displayed a broad absorption at 3374 cm⁻¹ attributable to ν(N-H) typical for the first row transition metal ammonia complexes.¹¹

Interestingly, attempts to isolate other Tp³Cu(NH₃) complexes using Tp³ ligands (Tp³ = Tp* or TpBr³) different from TpMs have failed. It seems that the steric protection provided by the mesityl substituent is crucial for the stability of the ammonia adduct.

Figure 1 shows the structure of the molecules of 1 as the result of X-ray diffraction studies. The complex is mononuclear, with the TpMs ligand coordinated in a κ³-N,N,N fashion and the NH₃ moiety bonded to the copper centre occupying the fourth coordination site of a slightly distorted tetrahedron formed by the four N donors. Additional comments on distances and angles are provided in the next section.

Table 1. List of selected bond distances [Å] and angles [°] for copper complexes 1-4.

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<td>118.85(13)</td>
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Synthesis and characterization of complexes Tp³Cu(NR₃) (2-5).

For the sake of comparison with the ammonia adduct 1 we have prepared a series of amine adduct of general composition Tp³Cu(NR₃) (Scheme 2) upon ligand exchange from Tp³Cu(THF) at room temperature. Crystalline materials were collected in 60-80% yield upon direct cooling of the reaction mixtures (see Experimental Section). These new copper-amine adducts are stable under vacuum in the solid state and even under air for short periods of time. Their spectroscopic and analytical data were in agreement with their formulation as the amine adduct of the Tp³Cu moiety.

X-ray studies carried out with complexes 2-4 have shown in all cases a distorted tetrahedral geometry around the copper centre. Figure 2 shows the ORTEP view of the molecules of 4 as a representative example (see ESI for those of complexes 2 and 3). Table 1 contains a list of selected bond distances and angles for complexes 1-4. The Cu(1)-N(pyr) (N1, N3 or N5) averaged 2.073 Å in 1, 2.08 Å in 2, 2.11 Å in 3 and 2.073 Å in 4. These values are slightly shorter than those found in the olefin adducts Tp³Cu(olefin) (2.15-2.21 Å)³ or in the alkyne adducts Tp³Cu(alkyne) (2.10 Å). This is probably the result of the exclusive sigma donation of the amine ligand to the metal centre in contrast with the back-bonding capabilities of both olefin and alkyne ligands. The Cu-N(amine) distance also deserves some comment. The Cu(1)-N(7) distance in 7 of 1.960(2) Å is similar to those previously found in CuCl(NH₃)(olefin) (1.987Å)¹²a or Cu(L)(NH₃) (1.973 Å, L = bidentate ligand).¹²b Such distance slightly increases when moving from 1 to 4, probably accounting for the augment of the steric volume of the amine ligand.
The relative reactivity of the above complexes toward amine exchange has been studied (Scheme 3). Thus, when complex 1 was reacted with one equiv of either diethyl or benzylamine, complete conversion into 3 or 4 was respectively observed whereas bubbling of ammonia through the solutions of 3-4 returned 1 in solution. From these results it seems reasonable proposing that the substituted amine provides more stable adducts albeit the difference in energy is not large given the possibility of reversion with excess of ammonia.

Ammonia N-H functionalization.

**N-H cleavage and N-C bond formation.** On the basis of the availability of the ammonia complex 1, we have studied its reactivity toward hydrogen abstraction, with the aim of the consecutive formal proton and hydride abstraction and final nitrene formation (Scheme 4). We planned the use of lithium disopropylamide (LDA) and a triphenylmethyl salt (Ph₃CPF₆) as respective proton and hydride scavengers. The one-pot reaction, either at low or room temperature, led to a somewhat dirty reaction mixture from which we have isolated two products: Tp₆Cu(NH₂CPh₃) (5) and Tp₆Li(THF) (6). Separate experiments carried out with 1 and LDA and Ph₃CPF₆, respectively, have afforded compounds 6 and 5, respectively (Scheme 4).

The formation of complex 5 from 1 and Ph₃CPF₆ escapes from the common role of hydride scavenger. Formally, the Ph₃C group replaces one of the H atoms of ammonia, HPF₆ being likely formed for reaction balance. Complex 5 was isolated in 16% yield from that reaction mixture as colourless crystals, some of them suitable for an X-ray diffraction studies. Figure 3 shows the ORTEP view where the formation of triphenylmethylamine is demonstrated. Moreover, this compound has been independently prepared upon reacting Tp₆Cu(THF) and commercial NH₂CPh₃ following the aforementioned procedure described for compounds 2-4 (see ESI). Spectroscopic, analytical and even structural data for both samples were identical.

The solid-state structure of 5 (Figure 3) has shown some interesting features. A similar, distorted tetrahedral geometry is observed around the copper centre for 1-5. However, in the case of 5 the values of the Cu-N(pyr) distances are somewhat larger: 2.34 Å for Cu(1)-N(1) and 2.301 Å Cu(1)-N(2), the third one yet resembling the values found for 1-4 (See Scheme 5).

In good agreement with this, two sets of resonances for the mesityl pyrazolyl units are observed in the NMR with relative ratio 2:1. In addition, a weak NOE effect has been detected between the NH₂ hydrogen nuclei and the aromatic resonances. These data support the proposal of a certain interaction of the NH₂ hydrogens with the π-system of the mesityl rings. This would preclude the rotation of the Cu-N(amine) bond, decreasing the symmetry of the molecule. To shed light on this idea, the related complex Tp₆Cu(NH₂CPh₂) (7) bearing diphenylmethylamine has been prepared and fully characterized, including X-ray studies (see ESI for full details). The absence of the third phenyl group in 7 decreases the steric pressure around the metal centre to such extend that the Cu-N(pyr) distances found are very similar to those already commented for complexes 1-4 (Scheme 5).
Complex $\text{Tp}^{\text{NH}}\text{Li}(\text{THF})$ (6) has been isolated as colourless crystals, from which NMR data showed the typical pattern of the coordinated $\text{Tp}^{\text{NH}}$ ligand as well as coordinated tetrahydrofuran. The observation of a slight difference in the chemical shifts and the lack of good elemental analysis prompted us to determine its X-ray structure from which the presence of lithium, and not copper, bonded to the ligands was assessed. The loss of copper could be related with the highly reductant power of LDA, albeit we have not been able to isolate any copper species from the reaction mixture. We believe that this finding is of interest for the researchers in the field of trispyrazolylborate-containing transition metal complexes, since this simple “transmetallation” is not expected.

**Scheme 5.** Comparison of bond distances (Å) around the copper centre for several complexes $\text{Tp}^{\text{NH}}\text{Cu}(\text{amine}),$

Ammonia NH functionalization by carbene insertion.

Last decade we reported on the catalytic insertion of carbene $\text{CHCO}_2\text{Et}$ units (from ethyl diazoacetate) into N-H bonds of several amines in good yields with several $\text{Tp}^{\text{Cu}}\text{L}$ complexes as the catalyst. In spite of the interest of this reactions, that lead to aminocarbonyl formation, its application to ammonia as the substrate is reduced to the work by Gross and co-worker with an iron-based catalyst. On the basis of this, we have now studied the catalytic potential of the complex $\text{Tp}^{\text{NH}}\text{Cu}(\text{THF})$ toward the reaction of ethyl diazoacetate and ammonia. The reaction was performed upon dissolving the catalyst in dichloromethane followed by saturation of the solution with ammonia gas. After 10 min of bubbling, EDA was slowly added with the aid of a syringe pump for 1h. After that time, the reaction mixture was stirred for additional 72h and the reaction was investigated by GCMS. A mixture of the two products derived from the formal insertion of one or two carbene groups into the N-H bonds of ammonia in relative ratio of 50:50 (Scheme 6) was observed, with an overall yield of >95% (EDA-based). These results brings copper into line with iron for the direct transformation of ammonia into glycine ester.

Gross and co-worker reported 13 on the mechanism of the iron-based reaction to occur with no formation of iron-carbene intermediates, at variance of many other metal-diazoacetate transformations. This is at variance with our $\text{Tp}^{\text{NH}}\text{Cu}$ based system, for which the copper-carbene intermediates have already been detected and spectroscopically characterized. From this $\text{Tp}^{\text{NH}}\text{Cu}=\text{C(H)}\text{CO}_2\text{Et}$ species, it is very likely that a N-ylide is formed, since a related transformation with esters and similar catalysts have revealed such behaviour. A final 1,2-shift from the ylide to the formal insertion product would account for the formation of the amino acid derivative.

![Scheme 6.](attachment:Scheme6.png)

Ammonia NH functionalization by carbene insertion. Bottom: plausible reaction pathway.

**Conclusions**

We have prepared and fully characterized the ammonia complex $\text{Tp}^{\text{NH}}\text{Cu}(\text{NH}_3)$ (1), that completes a series of $\text{Tp}^{\text{Cu}}\text{L}$ complexes ($\text{L} = \text{MeCN}, \text{CO}, \text{olefin, alkyne}$), a a series of related $\text{Tp}^{\text{NH}}\text{Cu}(\text{amine})$ complexes. The N-H bond of coordinated ammonia has been replaced with the bulkier Ph$_3$C group upon reaction with Ph$_3$CPF$_6$ yielding $\text{Tp}^{\text{NH}}\text{Cu}(\text{NH}_2\text{CPh}_3)$ in a rare example in which the tryt cation does not formally acts as hydride scavenger. The reaction of 1 with a strong base such as LDA induced the decomposition of 1 toward $\text{Tp}^{\text{NH}}\text{Li}(\text{THF})$, an unexpected case of transmetallation reaction. In addition to the above stoichiometric N-H functionalization, the first copper-catalyzed activation of ammonia N-H bonds has been achieved with $\text{Tp}^{\text{NH}}\text{Cu}(\text{THF})$ as the catalyst for the reaction with ethyl diazoacetate, leading to glycine derivatives.

**Experimental**

**General Methods.** All procedures were performed in a glovebox under an inert atmosphere of dinitrogen or using standard Schlenk techniques. All substrates were purchased.
from Sigma-Aldrich and used without further purification. Solvents were dried and degassed before use. The TpM(Cu)(THF)\(^{4+}\) complex was prepared according to literature methods. NMR spectra were recorded on Agilent 400 MR or Agilent 500 DD2, \(^1\)H and \(^{13}\)C NMR shifts are reported relative to tetramethylsilane. FT-IR spectra were collected on a Nicolet IR20 FTIR spectrometer. Elemental analyses were performed on a Perkin-Elmer Series II CHNS/O Analyzer 2400.

**Synthesis of TpM(Cu)(NH\(_2\))** (1). The complex TpM(Cu)(THF) (0.22 g, 0.31 mmol) was dissolved in dichloromethane (20 mL) and NH\(_2\)H was bubbled through the solution at room temperature for 10 min. The solution was cooled at -30°C leading to the isolation of colourless crystalline material in 95% yield after successive crops. Anal. Calc. for Cu\(_2\)H\(_2\)Cu\(_2\): C, 60.62; H, 6.19; N, 13.37. Found: C, 60.24; H, 6.21; N, 13.17. IR(KBr): ν(BH\(_2\) pyrazol), 1349, 1332 cm\(^{-1}\); ν(NH), 3472, 3332 cm\(^{-1}\).

**General synthetic protocol for complexes TpM(Cu)[amines]** (2-7). To a solution of complex TpM(Cu)(THF) (0.08 g, 0.114 mmol) in dichloromethane (15 mL) 4 equiv of the corresponding amine were added (0.34 mmol). After 5 min of stirring the solvent was concentrated and the solution cooled at -30°C from which colourless crystals of 2-5 were collected in 60-80% yield. The complex 1 was prepared in the same way but adding only one equivalent of amine. The crystallisation was performed in pentane (5-10 mL) to obtain yellow crystals. 43% YIELD.

**TpM(Cu)(ethylamine)** (2). Anal. Calc. for Cu\(_2\)H\(_2\)Cu\(_2\):C, 64.34; H, 6.73; N, 13.64. Found: C, 64.50; H, 6.75; N, 13.33. IR(KBr): ν(BH\(_2\) pyrazol), 1349, 1332 cm\(^{-1}\); ν(NH), 3472, 3332 cm\(^{-1}\); ν(C=O), 1684 cm\(^{-1}\).

**TpM(Cu)(diethylamine)** (3). Anal. Calc. for Cu\(_2\)H\(_2\)Cu\(_2\): C, 68.22; H, 7.30; N, 13.92. Found: C, 68.03; H, 7.63; N, 13.76. IR(KBr): ν(BH\(_2\) pyrazol), 1349, 1332 cm\(^{-1}\); ν(NH), 3472, 3332 cm\(^{-1}\); ν(C=O), 1684 cm\(^{-1}\).

**TpM(Cu)(benzylamine)** (4). Anal. Calc. for Cu\(_2\)H\(_2\)Cu\(_2\):C, 67.92; H, 6.53; N, 12.80. Found: C, 68.36; H, 6.47; N, 12.94. IR(KBr): ν(BH\(_2\) pyrazol), 1349, 1332 cm\(^{-1}\); ν(NH), 3472, 3332 cm\(^{-1}\); ν(C=O), 1684 cm\(^{-1}\).

**Isothermal of TpM(Li)(THF)** (6). This complex was isolated from the reaction of complex 1 (0.1 mmol) and LDA (0.1 mL of a 2 M solution in THF) or BuLi (0.08 mL of a 2.5 M solution in Hexane). The first method complex 1 was dissolved in dichloromethane (10 mL) and cooled to -50 °C. Next was added LDA. The reaction was stirred for 30 min. After was filtered and concentrated and cooled at -30°C. White-Brown crystals were obtained that correspond to compound 6 Yields 32%. the second method to solution of 1 in 15 mL of tetrahydrofuran was added 100 μL of BuLi.The reaction followed the same previous procedure to give white crystals. Yield 36%

**X-ray structure determination.** The structures of complexes 1-7 have been determined and deposited in the CCDC with the following codes: 1, CCDC-1443209; 2, CCDC-1443210; 3, CCDC-
Amine Exchange Reactions. A solution of TpCu(NH)3 (1) in 0.6mL of deuterated solvent dichloromethane was placed in a NMR tube and one equiv of the corresponding amine was added. NMR analysis showed the formation of 3 or 4 in a few minutes. Complex 1 was restored upon bubbling ammonia gas through the solution for several minutes.

Carbene transfer reaction from ethyl diazoacetate (EDA) to ammonia. A solution of TpCu(THF) (0.08 mmol) in dichloromethane 20 mL was saturated with ammonia upon gentle bubbling for 15 min. Then the NH3 supply was disconnected and a solution of EDA (1.6 mmol in 5 mL of dichloromethane) was slowly added for 1 h. After an overall 72 h time of stirring, the mixture was taken to dryness and the residue was investigated by NMR spectroscopy that show the exclusive formation of ethyl glycinate ester NH(CH2CO2Et) and the bis-functionalized product NH(CH2CO2Et)2 in ca. equimolar amounts (yields established by GCMS). No carbene dimers nor unreacted EDA was observed after that time.

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References


